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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,885	09/06/2006	Nicholas Gekakis	P1148US10	6952
29490 7590 12/29/2008 GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION 10675 JOHN JAY HOPKINS DRIVE, SUITE E225 SAN DIEGO, CA 92121-1127				
EXAMINER				
NOBLE, MARCIA STEPHENS				
ART UNIT		PAPER NUMBER		
1632				
NOTIFICATION DATE		DELIVERY MODE		
12/29/2008		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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### Office Action Summary

**Application No.**

10/591,885

**Applicant(s)**

GEKAKIS ET AL.

**Examiner**

MARCIA S. NOBLE

**Art Unit**

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) 1-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB-08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Status of Claims***

Claims 1-28 are pending.

### ***Election/Restrictions***

Applicant's election without traverse of Group III, claims 17-18, in the reply filed on 12/9/2008 is acknowledged.

Claims 1-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/9/2008.

Claims 17-28 are under consideration.

### ***Sequence Compliance***

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims,

even if the sequence is also embedded in the text or the description or claims of the patent application.

Figures 1B and 2 disclose sequences that do not have SEQ ID NOS that correspond to the Sequence Listing and CRF.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse comprising in its genome a nucleic acid a mutant prohormone convertase 1 (PC1) gene comprising a missense mutation at residue Asn222 in the catalytic domain operably linked to the endogenous PC1 promoter, does not reasonably provide enablement for the following:

- 1) any non-human animal other than a mouse comprising the claimed mutated gene;
- 2) a mouse comprising a mutated PC1 gene that is not stably integrated into its genome;
- 3) a mouse comprising a mutated PC1 gene that lacks operable linkage to a promoter; and

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

1) The claims encompass a non-human animal comprising a targeted mutation in its PC1 gene.

In a forward genetic screen of ENU-mutagenized mice, the inventors discovered two obese mutant mice comprising a substitution of Asn<sup>222</sup> with an Asp in PC1 gene. This substitution resulted in mutant mice having significantly greater body weight, body fat content, and insulin production as compared to wild type mice (Example 1, p. 22, [0086], line 1 to p. 23, line 4). The specification also discloses that the instant mice comprising this specific mutation can be produced by targeted introduction of a transgene into the PC1 gene using homologous recombination P. 18, lines 1-15).

At the time of filing and presently, gene-targeting in vivo required homologous recombination in cells in vitro. The only cells that can be cultured in vitro that are competent to populate the germline and make a mammal are mouse embryonic stem (ES) cells. Thus, ES cell use for germ-line, targeted genetic modification in mammals, such as is necessary for the production of knockout animals, has only been established in mice. This is evidenced by the teachings of Denning and Priddle (Reproduction 126:1-11. 2003) which states, "Gene targeting of an endogenous gene was first reported in mice by Smithies et al. (1985). This technology has since provided tremendous insight into a plethora of biological questions...and is the major basis of the desire to extend targeting to other species...However, pluripotent embryonic stem (ES) cells, which have been central to success in mice, are not available in any domestic species, despite considerable efforts to isolate them." (See p. 1, col 2, par 1, lines 1-12). Therefore, the art suggests that the production of targeted genetic modification, as used in knockin technologies, in any other species than mouse is unpredictable, as evidenced by Denning and Priddle. Therefore, the instant specification fails to enable the instantly claimed invention because the specification and art fail to provide specific guidance to predictably produce a non-human animal comprising the targeted mutation in its PC1 gene in any other species of mammal than a mouse.

2) The breadth of the claims encompasses introducing a transgenic into an animal that is not stably integrated into the genome. The specification discloses that the stable integration of the mutation in the PC1 is an essential structural feature of the claimed animal. Furthermore, the specification contemplates propagation of the mutant

mice and the production of homozygous mice for the mutation by breeding (p. 18, lines 1-22). Neither the specification nor the art teach a means of propagating an introduced mutation in an animal that has not been stably integrated into the genome.

Furthermore, the specification fails to provide a use for a non-human animal comprising a mutated PC1 gene that is not stably integrated into its genome. Therefore, the specification only enables a mutant animal comprising the claimed mutant PC1 gene in its genome.

3) The breadth of the claims encompass a transgenic animal comprising and expression a mutant PC1 gene that lacks operable linkage to a promoter. However, for a transgene to be expressed effectively it must minimally comprise the elements to direct the transcription and translation machinery of the target cell which require a promoter capable of driving expression in the target cell (Chen et al US 5,824,837 10/20/1998; see col 2, line 49-53). In the instant case, the specification discloses use of a targeting vector designed to replace a portion of the PC1 gene (p. 18, lines 6-8), therefore the specification teaches operable linkage to the endogenous PC1 promoter. Because of the necessity for the minimal elements necessary to drive expression of a gene, an artisan would not know how to use the claimed nucleic acid in an expression vector without operable linkage to a promoter. Therefore, the expression vector of claims would minimally require operable linkage to a promoter for the invention to function.

In summary, the instant claims lack enablement for the full breadth of the claims. The art suggests that the production of a non-human animal comprising a targeted

mutation is unpredictable and the specification and art only provides specific guidance to teach a mouse. The claims are also deemed to lack enablement because the claims lack essential elements, such as operable linkage to a promoter and stable integration into the genome, which are necessary for the function of the invention.

Therefore at the time of filing the skilled artisan would need to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 27, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhu et al. (PNAS 99(16):10293-10298, 2002).

Zhu et al discloses a mouse with a targeted deletion of exon 1 and several putative upstream transcription controls from the PC1 gene (p. 10294, col 1, last par, line 1 to col 2, line 1). Zhu et al discloses that expression of the PC1 eliminated in the mice that were homozygous for the disruption (p. 10294, col 2, lines 4-6). These disclosure encompass the limitations because a mouse that lacks expression of PC1 due to disruption of the gene inherently has a PC1 mutation that is defective in autocatalytic activity as claimed. The process of introducing a transgene that results in

a deletion of exon 1 would also encompass the limitations of introducing a heterologous transgene as claimed in claim 28.

Therefore, clearly, Zhu et al anticipates the instant claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-21 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackson et al (Nature Genetics 16:303-306, 1997) in further view of Gorman et al (US 6,348,327 Patent date: 2/19/2002), Capecchi et al (US 5,464,764 patent date:12/7/1995), and Cittadini et al (Circulation 100:2177-2183, 1999).

Jackson et al teaches that a mutant allele of PC1 that renders the PC1 defective and results in obesity, abnormal glucose homeostasis, hypogonadism, hypocortisolism, and elevated levels of proinsulin exists in the human population. More specifically, Jackson et al teaches mutations in exon 5 and Gly to Arg substitution at amino acid residue 483 of PC1 cause the defective allele (p. 303, col 1, par 1, lines 5-22).

Jackson et al does not teach the specific mutation of a substitution of Arg for Asp at residue 222 of PC1. However, Gorman et al teaches cells that are transfected with an expression vector encoding various mutations of mouse PC1 (col 38, lines 15-43).

Gorman et al discloses the cDNA and protein sequences for mouse PC1 (Fig 1 and 3, respectively). Gorman et al teaches that various mutations of the PC1 comprising substitution, deletions, or insertions can be prepared using oligonucleotide-mediated mutagenesis (col 16, line 47 to col 17, line 3). Therefore, Gorman et al teaches that the mouse PC1 sequence was established in the art and a desire and means of producing mutant forms of PC1 was also established in the prior art.

Jackson et al also does not teach a non-human animal comprising this missense substitution mutation. Cappechi et al teaches a means of introducing an exogenous sequence into a specific target sequence into the genome of a mouse by homologous recombination and using a positive negative selection expression vector (col 15, line 59- col 16, line 10). This method allows for the introduction of a type of mutation into a specific gene sequences. Therefore, Cappechi et al teaches that a means of introducing a specific gene mutation into a mouse was established in the prior art.

Furthermore, Cittadini et al teaches that Obesity is a common disease associated with increased morbidity and mortality and is responsible for 7.8% of all healthcare costs (p. 2177, col 1, lines 1-3). Cittadini et al further teaches a need for more obesity animal models to further understand the factors causing obesity and because present models are necessarily representative of pathologies associated with human onset of obesity (p. 2177, col 1, line 1 to col 2, line 6). Therefore, Cittadini et al established a need or rationale for producing more animal models of obesity.

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. \_\_\_, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary

skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the present situation, rationales A, E, and G are applicable. It would have been obvious to an artisan of ordinary skill at the time the invention was made to choose from a finite number of nucleic acid encoding missense mutation in the mouse PC1 gene to predictably yield a mutant mouse harboring a missense mutation of Asn222 to Asp in PC1 with a reasonable expectation of success. The prior art establishes that PC1 missense mutation have resulted in obesity in the human population, as taught by Jackson. The prior art also teaches a need for more animal models to study obesity that are applicable to the human condition, as taught by Cittadini et al. Thus, the art provides reasoning to target PC1 gene with missense mutations in an animal model to potentially further investigate factor involve in human obesity. The prior art of making various mutations in PC1 genes was established in the prior art, as taught by Gorman et al, as well as the means to produce mice harboring the specific mutations, as taught by Capecchi et al. Therefore, an artisan would have a reasonable expectation of predictably yielding the claimed non-human mutant animal because the means of making the animal were established in the prior art.

Thus, the teachings of the cited prior art in the obviousness rejection above provide the requisite teachings and motivations with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

This rejection might be overcome by insertion of a phenotype associated with the disruption presenting in the claimed transgenic nonhuman animals.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/  
Primary Examiner, Art Unit 1632

Marcia S. Noble  
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